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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/226,895	01/07/99	ROSENBLUM	M D6205

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/226,895	Rosenblum et al
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or ~~thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-11* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

2. The disclosure is objected to because of the following informalities: Table 1 is included as a drawing but should be incorporated within the text of the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5 and 10 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

-Claim 5 recites an improper Markush group. The applicant is referred to MPEP § 706.03(y) and advised to reformat the claim to read "wherein said retinoid is a material selected from the group consisting of ....(TTNPB) **and** (E)-4-[2-95,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-nephthalenyl)-1-propenyl]benzoic acid (3-met TTNPB)."

-Claim 10 recites an improper Markush group. The applicant is referred to MPEP § 706.03(y) and advised to reformat the claim to read "wherein the monoclonal antibody is a material selected from the group consisting of IB4 **and** IB6".

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of retinoids to up-regulate CD38 antigen as a cellular target, and the use of monoclonal antibody-conjugates specific to the up-regulated CD38 antigen as a method of treating certain types of leukemias, does not reasonably provide enablement for all possible pathophysiological conditions, all possible antigenic stimulating agents, nor all possible immunotoxins directed toward the up-regulated antigens. The state of the art encompasses methods for treatment of cancers comprising the administration of interferon alpha to up-regulate the tumor antigens COL-1 and TAG-72 and the administration of specific immunotoxins, COL-1 and CC49, targeting those antigens. The prior art does not contain any reference to this type of method for the treatment of other pathophysiological state except cancer. Claim 1 recites no limitations on the types of pathophysiological states to which this method could be applied with

efficacy. The specification provides no guidance for the treatment of any pathophysiological condition except leukemias, lymphomas and myelomas. The current art teaches a growing number of tumor specific antigens. Those skilled in the art could target these alternative tumor antigens, but given the unpredictability of finding an agent which would increase the density of the desired antigen predominately on tumor cells without causing deleterious effects on the individual, the expectation of success would be low without further guidance. Claim 1 recites no limitations on the type of agents that could be administered, and the specification provides no guidance other than the use of retinoids. Also, the language in claim 1 does not restrict the up-regulated cellular target to an extracellular or intracellular location or to cellular targets that are not expressed in the cell before the administration of the agent. There is no guidance given in the specification for up-regulating and targeting via immunotoxin intracellular targets, or targets that are not expressed in tumor cells before the administration of the inducing agent. Claim 1 recites no limitations on the nature of the immunotoxin. It is well known in the art that the nature of the target, the antibody-conjugate and the cell type expressing the target are unpredictable as to the suitability of each to a method of treatment. Antibody-conjugates which differ in the toxin they deliver have widely differing efficacies due to the nature of the chemistry which binds the toxin to the antibody, the toxin itself, and the nature of the interaction of the antibody with the cellular target. Antibody-conjugates binding a cellular antigen which is not efficiently internalized will not show marked

cellular toxicity. It is well know in the art that antibodies can be raised to differing epitopes of a protein. Antibodies can be found to receptors which activate an intracellular processes as well as block or neutralize such a processes. In the absence of efficient internalization of the antibody for toxin delivery, one could inadvertently activate unwanted cell division and expansion of a tumor. The toxin itself can be modified enzymatically or chemically cleaved away from the antibody when administered in vivo. Cell types vary in their sensitivities to toxins. Without further direction from the specification or undue quantity of experimentation, one skilled in the art would not know what to administer as an immunotoxin (which specific monclonal antibody and which toxin) that would be efficacious for any cellular target. In view of the broad nature of this claim encompassing all pathophysiological states in all individuals, the unpredictablilty of the two steps of the claimed method (administration of agents which up-regulate cellular targets and administration of immunotoxins directed towards those up-regulated targets) as a method of treatment, the state of the current art limiting the above method to cancer treatment with interferon alpha and COL-1 and CC49, the lack of detailed guidance from the specification, undue experimentation would be necessary to extend this method beyond what is known in the art.

7. Claim 10 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 10 is rejected under 35 USC 112, first paragraph as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are know and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the hybridoma cell line producing the monoclonal antibodies IB4 and IB6. It is not clear that monoclonal antibodies possessing the identical properties of IB4 and IB6 are known and are publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredicatable event. Although the applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtained the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the availability to practice the invention as claimed in the absence of the availability of the claimed monoclonal antibodies, IB4 and IB6, a suitable deposit of the hybridomas producing IB4 and IB6 for patent purposes, evidence of public availability of hybridomas producing IB4 and IB6, or evidence of reproducibility without undue experimentation of the claimed monoclonal antibodies is required.

Applicant's referral to the deposit of hybridomas producing the monoclonal antibodies IB4 and IB6 as disclosed on page 11 of the specification is s an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met.

If the deposits of hybridomas producing the monoclonal antibodies IB4 and IB6 are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposits of hybridomas producing the monoclonal antibodies IB4 and IB6 have been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit of hybridomas producing the monoclonal antibodies IB4 and IB6 will be replaced if viable samples cannot be dispensed from the depository as

required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of hybridomas producing the monoclonal antibodies IB4 and IB6 are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CRF 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his/her signature and registration number averring:

(a) during the pendancy of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced should they become non-viable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibodies IB4 and IB6 as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing identical monoclonal antibodies IB4 and IB6 described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Meridith (Clinical Cancer Research 2:1811, 1996). Meridith discloses a method to of treating an individual having a pathophysiological state (specifically metastatic colorectal cancer) comprising the step of administering an agent which up-regulates the expression of a cellular target (specifically interferon alpha administration to up-regulate the cellular targets of carcinoembryonic antigen [CEA] and TAG-72), and the administration of immunotoxin directed toward the up-regulated cellular target (specifically radio-labeled antibodies COL-1 [anti-CEA] and CC49 [anti-TAG-72]) that is the same as that claimed.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-3, 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (Proceedings of the American Association for Cancer research 38: 88, 1997) in view of Hirota (Cancer Research 49: 7106-7109, 1989). Mehta discloses a method of killing leukemia cells in culture by administering retinoic acid to up-regulate the expression of the CD38 antigen, followed by administering a monoclonal antibody-gelonin conjugate specific for the up-regulated CD38 receptor. Mehta does not teach a method of treating an individual having a pathophysiological state. Hirota teaches a method of killing squamous cell carcinoma both in cell culture and in an individual having a pathophysiological state by administering interferon alpha to up-regulate epidermal growth factor-receptor, the cellular target, followed by the administration of B4G7-gelonin conjugate, a monoclonal antibody (the immunotoxin specific for the epidermal growth factor receptor) in a dose of 0.05mg/kg to 2.5mg/kg. The method taught by Mehta is exactly the same as what is recited in claims 1-3 and 7-10 with the exception of being carried out with cells in culture vs. in an individual having a pathophysiological state.

At the time the invention was made it would have been obvious to a person of ordinary skill in the art to apply the method of selective cell killing after up-regulation of a specific cell target in cell culture as disclosed by Metha to the method of treating an individual having a pathophysiological state as in claim 3. Hirota teaches a method of up-regulating a cellular target followed by administration of a specific monoclonal antibody conjugated to gelonin in a dose range of 0.05mg/kg to 2.5mg/kg as an effective method of targeting cells both in culture and in an individual.

One of ordinary skill in the art would have been motivated to extend the cell culture method disclosed by Mehta to the method of treating an individual in the instant case with a reasonable expectation that the cell culture method would be an effective method for the selective targeting of immunotoxins to up-regulated cellular targets in an individual.

13. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (Proceeding of the American Society for Cancer Research, **1997**, 38, page 88) and Hirota (Cancer Research 49: 7106-7109, 1989) as applied to claims 1-3 and 7-11 above, and further in view of Mehta (Proceeding of the American Society for Cancer Research, **1994**, 35 page 92).

Mehta in **1997** disclosed the method of administering retinoids to up-regulate the expression of CD38 in several leukemia cells and cell lines followed by the administration of a

specific immunotoxin (anti-CD38 conjugated to gelonin) but did not teach the specific type of retinoid as recited in claim 5 or dose of about 0.1 mg/kg to about 2 mg/kg as recited in claim 6 and did not cary out the method in individuals having the pathophysiological state of leukemias, lymphomas and myelomas as recited in claim 4. Hirota taught the successful translation of a similar method directed toward killing cells in culture to a method for eradicating tumor cells in an individual having a pathophysiological state as discussed above. Mehta in **1994** teaches "In four patients with acute promyelocytic leukemia, a significant increase in CD38 expression was observed *in vivo* following administration of a single oral dose (45mg/m^2) of ATRA (all-*trans* retinoic acid)" thereby teaching the effectiveness of the method comprising administering all-*trans* retinoic acid, as recited in claim 5, to individuals having the pathophysiological state of acute promyelocytic leukemia as recited in claim 4. The dose of retinoic acid taught by Mehta in 1994 of 45mg/m^2 of all-*trans* retinoic acid lies within the range of claim 6 which recites that the retinoid is administered in a dose of about 0.1 mg/kg to about 2mg/kg. Thus it would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the retinoid as all-*trans* retinoic acid in the cited dose range. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mehta, and teachings well known in the art that such optimization of dosages is

routine, of the administration of all-*trans* retinoic acid in a dosage of 45mg/m^2 to individuals having the pathophysiological state of acute promyelocytic leukemia.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzel, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

February 24, 2000